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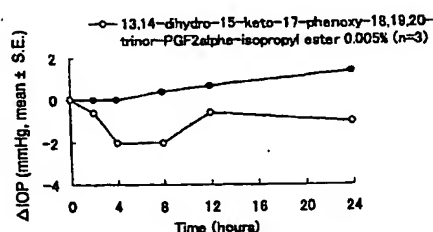
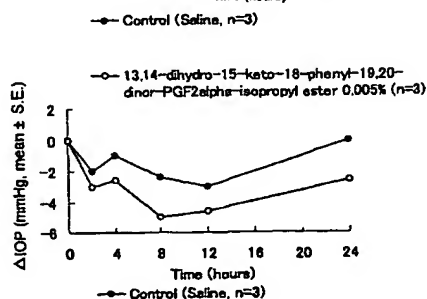
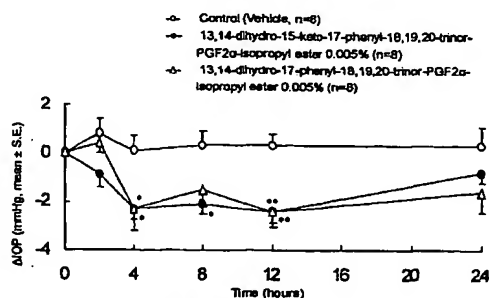
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[Continued on next page]

(54) Title: METHOD AND COMPOSITION FOR TREATMENT OF OCULAR HYPERTENSION AND GLAUCOMA



(57) Abstract: Provided is a method for treating ocular hypertension and glaucoma, which comprises administering an effective amount of 15-keto-prostaglandin compound having a ring structure at the end of the ω chain to the eyes of a mammalian subject in need of such treatment once a day. According to the method, single administration of the compound effectively lower the IOP of the subject throughout the day.

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## DESCRIPTION

METHOD AND COMPOSITION FOR TREATMENT OF  
OCULAR HYPERTENSION AND GLAUCOMA

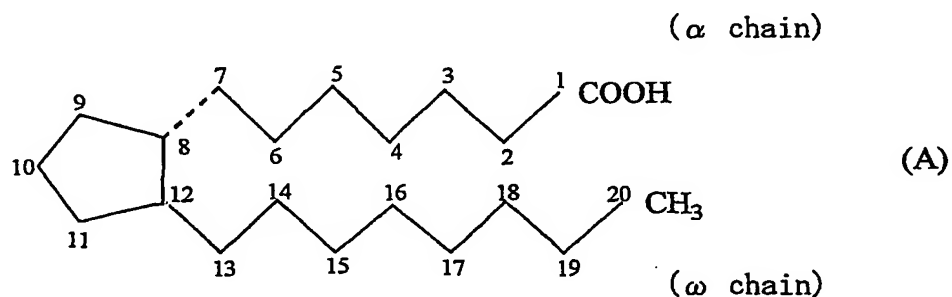
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## Technical Field

The present invention relates to a method for treating ocular hypertension and glaucoma of a mammalian subject. The present invention also provides a composition useful  
10 for the treatment.

## Background Art

Prostaglandins (hereinafter, referred to as PG(s)) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs  
15 found in nature (primary PGs) generally have a prostanoic acid skeleton as shown in the formula (A):



On the other hand, some of synthetic analogues of  
20 primary PGs have modified skeletons. The primary PGs are classified to PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs,

PGHs, PGIs and PGJs according to the structure of the five-membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond at the carbon chain moiety:

- 5           Subscript 1: 13,14-unsaturated-15-OH  
            Subscript 2: 5,6- and 13,14-diunsaturated-15-OH  
            Subscript 3: 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

10           Further, the PGFs are classified, according to the configuration of the hydroxyl group at the 9-position, into  $\alpha$  type (the hydroxyl group is of an  $\alpha$ -configuration) and  $\beta$  type (the hydroxyl group is of a  $\beta$ -configuration).

15           PGE<sub>1</sub>, PGE<sub>2</sub> and PGE<sub>3</sub> are known to have vasodilation, hypotension, gastric secretion decreasing, intestinal tract movement enhancement, uterine contraction, diuretic, bronchodilation and anti ulcer activities. PGF<sub>1 $\alpha$</sub> , PGF<sub>2 $\alpha$</sub>  and PGF<sub>3 $\alpha$</sub>  have been known to have hypertension, vasoconstriction, intestinal tract movement enhancement, uterine contraction, lutein body atrophy and  
20           bronchoconstriction activities.

            PGF<sub>2 $\alpha$</sub>  has a strong affinity with FP receptor, which is one of PG receptors, and has intraocular pressure reducing effects. However, ocular administration of PGF<sub>2 $\alpha$</sub>  or an ester thereof will cause transient IOP increase, and  
25           because of such side effects as strong hyperemia in

conjunctiva and iris, lacrimation, eye mucus, lid closure, etc.,  $\text{PGF}_{2\alpha}$  cannot be clinically employed.

"Xalatan®" eye drops that has been launched as a pharmaceutical composition for treatment of ocular hypertension and glaucoma contains, as its active ingredient, latanoprost, which is a PG derivative having hydroxy group at the 15-position, i.e., 13,14-dihydro-17-phenyl-18,19,20-trinor- $\text{PGF}_{2\alpha}$ -isopropyl ester. Like  $\text{PGF}_{2\alpha}$ , latanoprost has a strong affinity with the FP receptor and can reduce the IOP throughout the day by ocular administration once a day.

Some 15-keto (i.e., having oxo group at the 15-position instead of the hydroxyl group)-PGs and 13,14-dihydro (i.e., single bond between the 13-position and the 14-position)-15-keto-PGs are the substances naturally produced by the action of enzymes during the metabolism of the primary PGs. It is also known that some 15-keto-PG compounds have IOP reducing effects and are effective for treatment of ocular hypertension and glaucoma (U.S. Patent Nos. 5,001,153; 5,151,444; 5,166,178 and 5,212,200, all of which are incorporated herein by reference).

It has been known that the 15-keto-PG compound has substantially no affinity with the FP receptor. For example, "Rescula®" eye drops that has been launched as a pharmaceutical composition for treatment of ocular

hypertension and glaucoma contains, as its active ingredient, isopropyl unoprostone, which is a metabolic prostaglandin analogue having keto at the 15-position, i.e., 13,14-dihydro-15-keto-20-ethyl-  $\text{PGF}_{2\alpha}$ -isopropyl ester and  
5 has substantially no effect on the FP receptor and other PG receptors. In order to lower the IOP throughout a day, it is necessary to administer isopropyl unoprostone at least twice a day.

In this way, it has been considered to be difficult to  
10 provide daylong IOP lowering effect by single administration of the metabolic PG analogue having keto at the 15-position.

Meanwhile, from the viewpoint of the side effects, the present inventor has already found that compounds having  
15 substantially or practically no affinity with the FP receptor and other PG receptors, containing PG compounds having keto at the 15-position, cause substantially no iris pigmentation (U.S. Patent Application Publication No. 20020022644) and substantially no ocular irritation such as  
20 conjunctival hyperemia or the like. (U.S. Provisional Patent Application No. 60/308,589). These cited references are herein incorporated by reference.

However, "Xalatan®" eye drops containing latanoprost having hydroxy group at the 15-position has a strong  
25 affinity with the FP receptor and also has an affinity with

other PG receptors such as EP receptor. For this reason, problematic side effects of "Xalatan®" eye drops in clinically applied dose have been reported, including iris pigmentation, ocular irritation such as conjunctival hyperemia and chemosis of conjunctiva (American Journal of Ophthalmology 2001;131:631-635, Survey of Ophthalmology 1997; 41: S105-S110, the cited reference is herein incorporated by reference).

Therefore, in treating ocular hypertension and glaucoma, it has been desired to develop a pharmaceutical composition that can effectively lower the IOP of a subject and keep the low IOP throughout a day by once-a-day administration with substantially no or reduced side effects.

#### DISCLOSURE OF THE INVENTION

The present inventor has conducted intensive studies on the biological activity of 15-keto-prostaglandin compounds and has found that a 15-keto-prostaglandin compound having a ring structure at the end of the  $\omega$  chain can effectively lower the IOP throughout a day in a mammalian subject by administering the same topically to the eyes once a day, and completed the present invention.

Accordingly, the present invention relates to a method for treating ocular hypertension and glaucoma, which comprises administering an effective amount of a 15-keto-prostaglandin compound having a ring structure at the end

of the  $\omega$  chain to the eyes of a mammalian subject in need of such treatment once a day.

The present invention also relates to an ophthalmic composition for treating ocular hypertension and glaucoma of a mammalian subject, which comprises an effective amount of a 15-keto-prostaglandin compound having a ring structure at the end of the  $\omega$  chain, wherein said composition is to be administered to the eyes of the subject once a day.

The present invention further relates to use of a 15-keto-prostaglandin compound having a ring structure at the end of the  $\omega$  chain for manufacturing an ophthalmic composition for treating ocular hypertension and glaucoma of a mammalian subject, wherein said composition is to be administered to the eyes of the subject once a day.

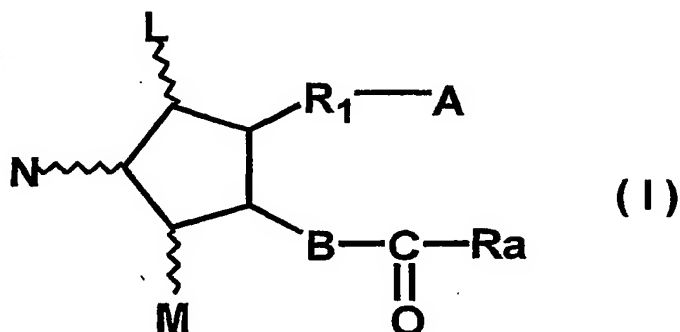
In the present invention, the "15-keto-prostaglandin compound" (hereinafter, referred to as "15-keto-PG compound") may include any of derivatives or analogs (including substituted derivatives) of a compound having an oxo group at 15-position of the prostanoic acid skeleton instead of the hydroxy group, irrespective of the configuration of the five-membered ring, the number of double bonds, presence or absence of a substituent, or any other modification in the  $\alpha$  or  $\omega$  chain.

The nomenclature of the 15-keto-PG compounds used



herein is based on the numbering system of the prostanoic acid represented in the above formula (A).

A preferred compound used in the present invention is represented by the formula (I):



5

wherein,

L, M and N are hydrogen atom, hydroxy, halogen atom, lower alkyl, hydroxy(lower)alkyl or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

10

A is  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

B is  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ ;

$\text{R}_1$  is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and one or more carbon atoms in the aliphatic hydrocarbon residue may optionally be replaced by oxygen, nitrogen or sulfur atom; and

15

20

$\text{Ra}$  is a saturated or unsaturated lower or medium

aliphatic hydrocarbon residue, at the end of which is substituted with cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.

#### BRIEF DESCRIPTION OF THE DRAWINGS

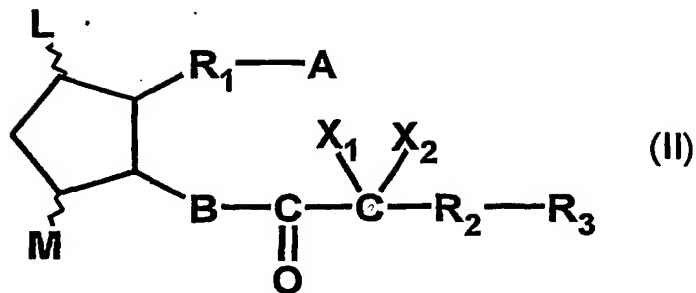
5        Fig. 1 shows effects of topical application of 0.005% 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF<sub>2α</sub>-isopropyl ester eye drops and 0.005% 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF<sub>2α</sub>-isopropyl ester eye drops on the IOP in Normal Monkeys: Changes in the IOP from time 0 (Δ IOP) are shown. \*\**p* < 0.01, \**p* < 0.05 compared to control (Dunnett's test).

      Fig. 2 shows effect of topical application of 0.005% 13,14-dihydro-15-keto-18-phenyl-19,20-dinor-PGF<sub>2α</sub>-isopropyl ester eye drops on the IOP in Normal Monkeys: Changes in the IOP from time 0 (Δ IOP) are shown.

      Fig. 3 shows effect of topical application of 0.005% 13,14-dihydro-15-keto-17-phenoxy-18,19,20-trinor-PGF<sub>2α</sub>-isopropyl ester eye drops on the IOP in Normal Monkeys: Changes in the IOP from time 0 (Δ IOP) are shown.

#### 20    PREFERRED EMBODIMENT OF THE INVENTION

      A group of particularly preferable compounds among the above-described compounds is represented by the formula (II):



wherein L and M are hydrogen atoms, hydroxy, halogen atoms, lower alkyl, hydroxy(lower)alkyl or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

A is  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

B is  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{C}\equiv\text{C}-$ ;

10  $\text{X}_1$  and  $\text{X}_2$  are hydrogen, lower alkyl, or halogen;

$\text{R}_1$  is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and one or more carbon atoms in the aliphatic hydrocarbon residue may optionally be replaced by oxygen, nitrogen or sulfur atom;

$\text{R}_2$  is a single bond or lower alkylene; and

$\text{R}_3$  is cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.

20 In the above formula, the term "unsaturated" in the definitions for  $\text{R}_1$  and  $\text{R}_2$  is intended to include one or more

double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 6 to 10 carbon atoms for  $R_1$  and 1 to 10, especially 1 to 8 carbon atoms for  $R_a$ .

The term "halogen atom" covers fluorine, chlorine, bromine and iodine.

The term "lower" throughout the specification is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O-, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

5       The term "lower alkanoyloxy" refers to a group represented by the formula  $\text{RCO-O-}$ , wherein  $\text{RCO-}$  is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

10       The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

15       The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O-, wherein cyclo(lower)alkyl is as defined above.

20       The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, and xylyl. Examples of the substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula  $\text{ArO-}$ , wherein Ar is aryl as defined above.

25       The term "heterocyclic group" may include mono- to

tri-cyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolinyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolinyl, benzothiazolyl and phenothiazinyl groups. Examples of the substituent include halogen and halogen substituted lower alkyl group, wherein halogen and lower alkyl group are those as described above.

The term "heterocyclic-oxy group" means a group represented by the formula  $\text{HcO-}$ , wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as

sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethyl- monoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether;

optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-dimethoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower)alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula  $-\text{CONR}'\text{R}''$ , wherein each of  $\text{R}'$  and  $\text{R}''$  is hydrogen atom, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide;



and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonyl-amide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy which has a 5-membered ring structure of, so-called, PGF type.

Preferred A is  $-\text{COOH}$ , its pharmaceutically acceptable salt, ester or amide thereof.

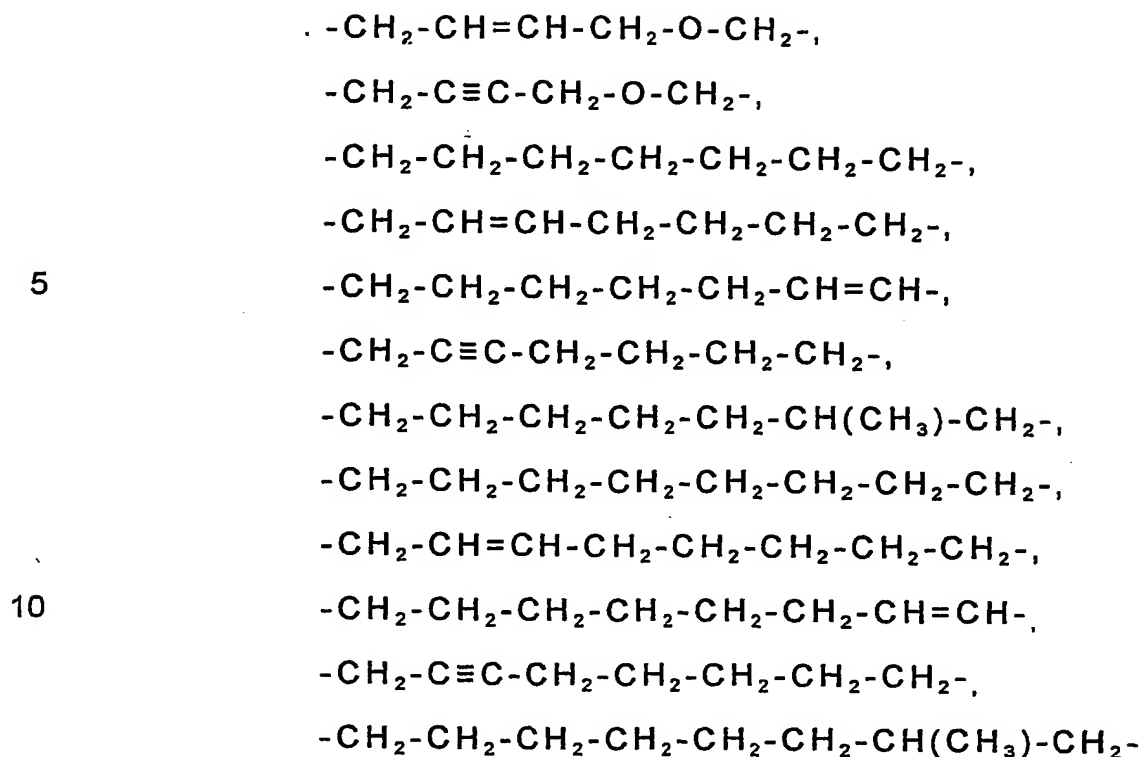
Preferred B is  $-\text{CH}_2-\text{CH}_2-$ , which provides the structure of so-called, 13,14-dihydro type.

Preferred example of  $X_1$  and  $X_2$  is that at least one of them is halogen, more preferably, both of them are halogen, especially, fluorine that provides a structure of, so called 16,16-difluoro type.

Preferred  $R_1$  is a hydrocarbon residue containing 1-10 carbon atoms, preferably, 6-10 carbon atoms. One or more carbon atoms, preferably one carbon atom on  $R_1$  may optionally be replaced by oxygen, nitrogen or sulfur atom.

Examples of  $R_1$  include, for example, the following groups:

$-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-$ ,  
 $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-$ ,



15  
 Preferred Ra is a hydrocarbon residue containing 1-10 carbon atoms, more preferably, 1-8 carbon atoms at the end of which is substituted with aryl or aryloxy.

20  
 The configuration of the ring and the  $\alpha$ - and/or  $\omega$  chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

25  
 Typical example of the compound used in the present invention is a 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-prostaglandin F compound, 13,14-dihydro-15-keto-18-phenyl-19,20-dinor-prostaglandin compound, 13, 14-

5 dihydro-15-keto-17-phenoxy-18,19,20-trieno-prostaglandin compound and their derivatives or analogues.

The 15-keto-PG compound of the present invention may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and oxo at position 15.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the 15-keto-PG compounds used in the invention include both isomers. Further, while the compounds used in the invention may be represented by a structure formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the hemiacetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used for the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in USP Nos. 5,073,569, 5,166,174, 5,221,763, 5,212,324, 5,739,161 and

6,242,485 (these cited references are herein incorporated by reference).

5 The term "treatment" used herein includes any means of control such as prevention, care, relief of the condition, attenuation of the condition, arrest of progression of the condition.

10 The term "a subject in need of such treatment" means a subject who is suffering from a disease in which a reduction in his/her intraocular pressure is desirable, for example, glaucoma and ocular hypertension, or a subject who is susceptible to suffering from such disease as discussed above. The subject may be any mammalian subject including human beings.

15 According to the present invention, the 15-keto-PG compound defined as above may be formulated as an ophthalmic composition and applied once a day topically to the eyes of a mammalian subject. The ophthalmic composition of the present invention may be any form for topical eye administration used in the ophthalmic field such as eye drops and eye ointment. The ophthalmic composition may be prepared in a conventional manner known to the art.

25 Eye drops may be prepared by dissolving the active ingredients in a sterile aqueous solution such as saline and buffering solution, or an eye drop composition may be the

one provided as a combined powder composition comprising the active ingredient to be dissolved in the aqueous solution before use.

Eye drops such as the ones as described in EP-A-  
5 0406791 are preferably used in the present invention (the cited reference is herein incorporated by reference). If desired, additives ordinarily used in conventional eye drops may be added. Such additives may include isotonizing agents (e.g., sodium chloride), buffering agent (e.g., boric  
10 acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate), preservatives (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol), thickeners (e.g., saccharide such as lactose, mannitol, maltose; hyaluronic acid or its salt such as sodium hyaluronate, potassium  
15 hyaluronate; mucopolysaccharide such as chondroitin sulfate; sodium polyacrylate, carboxyvinyl polymer, crosslinked polyacrylate.)

The eye drops may be formulated as a sterile unit dose type eye drops containing no preservatives.

20 Eye ointment may also be prepared in a conventional manner known to the art. For example, it may be prepared by mixing the active ingredient into a base component conventionally used for known eye ointments under a sterile condition. Examples of the base components for the eye  
25 ointment include petrolatum, selen 50, Plastibase and

macrogol, but not limited thereto. Further, in order to increase the hydrophilicity, a surface-active agent can be added to the composition. The eye ointment may also contain the above-mentioned additives such as the  
5     preservatives and the like, if desired.

The amount of administration of the active ingredient used in the present invention may vary according to the sex, age and weight of the subject, symptoms to be treated, effects of treatment to be desired, administration methods,  
10     period of treatment and the like. Typically, an eye drop composition containing 0.0001% - 10% of the active ingredient may be instilled once a day. In the case of using an eye ointment composition, a composition containing 0.0001% - 10% of the active ingredient may be applied once  
15     a day.

The ophthalmic composition of the invention may contain a single active ingredient or a combination of two or more active ingredients. In a combination of plural active ingredients, their respective contents may be  
20     suitably increased or decreased in consideration of their therapeutic effects and safety.

Further, the composition of the present invention may suitably include other pharmacologically active ingredients as far as they do not contradict to the object of the present  
25     invention.

According to the present invention, once-a-day administration of the ophthalmic composition of the invention can lower the IOP throughout the day. In addition, as already found out by the present inventors, the above-  
5 defined 15-keto prostaglandin compounds cause substantially no iris pigmentation, nor ocular irritation such as conjunctival hyperemia or the like.

The present invention will be described in more detail with reference to the following examples, which, however,  
10 are not intended to limit the present invention.

#### Example 1

##### 1) Test Method

Male cynomolgus monkeys (eight monkeys, body weights 3.0-4.5kg) were used. To the right eyes of the  
15 monkeys, 30  $\mu$  L/eye of 0.005% 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF<sub>2 $\alpha$</sub> -isopropyl ester eye drops, 0.005% 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF<sub>2 $\alpha$</sub> -isopropyl ester (latanoprost) eye drops or the vehicle was administered once with an interval of at least seven days,  
20 and the IOPs in the respective animals was measured.

##### 2) Measurement of IOP

The animals were retained in the sitting position under systemic anesthesia with intramuscular injection of ketamine hydrochloride (Ketalar® 50, Sankyo Co. Ltd.) 7.5-  
25 10mg/kg and their ocular surfaces were anesthetized with

0.4% oxybuprocaine hydrochloride (Benoxil® 0.4% solution, Santen Pharmaceuticals Co., Ltd.). After that, the IOP was measured with a pneumatonometer (Model 30 Classic, Mentor O & O, Inc.). The IOP was measured before (0 hour) and at 2, 4, 8, 12 and 24 hours after the administration of the test substances.

### 3) Statistical Analysis

Changes of the IOP from that of time 0 ( $\Delta$ IOP) obtained in the each test groups were compared to that obtained in the vehicle-administered control group at each measurement times. Statistical analysis was made with the Dunnett's multiple comparison test. Critical rates less than 5% were evaluated to be statistically significant.

### 4) Result

Results were shown in Fig. 1. Single administration of 0.005% 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF<sub>2 $\alpha$</sub> -isopropyl ester eye drops significantly lowered the IOP at 4, 8 and 12 hours after the administration by  $2.3 \pm 0.4$ ,  $2.1 \pm 0.4$  and  $2.4 \pm 0.5$  mmHg, respectively.

At any time point of the measurement, there were no significant difference between the  $\Delta$ IOPs of 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF<sub>2 $\alpha$</sub> -isopropyl ester group and those of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF<sub>2 $\alpha$</sub> -isopropyl ester (latanoprost) group. Accordingly, the two substances showed similar IOP



lowering effect in terms of strength and duration of the effect.

This result indicates that 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-PGF<sub>2α</sub>-isopropyl ester can lower the IOP and keep the low IOP throughout the day by single administration.

## Example 2

### 1) Test Method

Male cynomolgus monkeys (eight monkeys, body weights 3.0-4.5kg) were used. To the right eyes of the monkeys, 30  $\mu$  L/eye of 0.005% 13,14-dihydro-15-keto-18-phenyl-19,20-dinor-PGF<sub>2α</sub>-isopropyl ester eye drops or 0.005% 13,14-dihydro-15-keto-17-phenoxy-18,19,20-trinor-PGF<sub>2α</sub>-isopropyl ester eye drops were administered, and to the left eyes, 30  $\mu$  L/eye of saline was administered. IOP of the animals were determined.

### 2) Measurement of IOP

The animals were retained in the sitting position under systemic anesthesia with intramuscular injection of ketamine hydrochloride (Ketalar® 50, Sankyo Co. Ltd.) 7.5-10mg/kg and their ocular surfaces were anesthetized with 0.4% oxybuprocaine hydrochloride (Benoxil® 0.4% solution, Santen Pharmaceuticals Co., Ltd.). After that, the IOP was measured with a pneumatonometer (Model 30 Classic, Mentor O & O, Inc.). The IOPs were measured before (0

hour) and at 2, 4, 8, 12 and 24 hours after the administration of test substances.

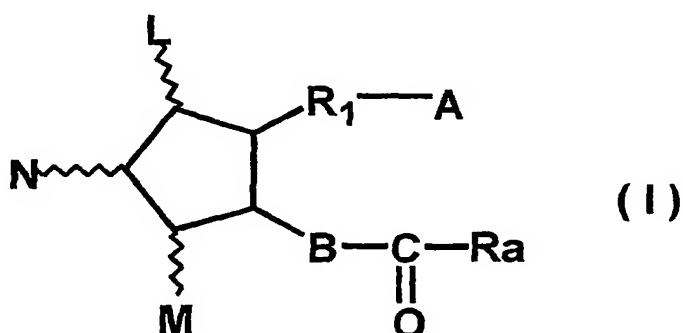
### 3) Result

Changes of the IOP from that of time 0 ( $\Delta$ IOP) obtained in the each test eyes (left eyes) were compared to those obtained in the vehicle administrated eyes (control group) at each measurement times. Results were shown in Fig. 2 and Fig. 3.

These results indicate that both of 13,14-dihydro-15-keto-18-phenyl-19,20-dinor-PGF<sub>2 $\alpha$</sub> -isopropyl ester and 13,14-dihydro-15-keto-17-phenoxy-18,19,20-trinor-PGF<sub>2 $\alpha$</sub> -isopropyl ester can lower the IOP and keep the low IOP throughout a day by single administration.

## CLAIMS

1. A method for treating ocular hypertension and glaucoma, which comprises administering an effective amount of 15-keto-prostaglandin compound having a ring structure at the end of the w chain to the eyes of a mammalian subject in need of such treatment once a day.
2. The method as described in Claim 1 wherein the 15-keto-prostaglandin compound is a compound represented by the following formula (I):



10

wherein L, M and N are hydrogen atom, hydroxy, halogen atom, lower alkyl, hydroxy(lower)alkyl or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

15

A is  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

B is  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ ;

$\text{R}_1$  is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is

20

unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and one or more carbon atoms in the aliphatic hydrocarbon residue may optionally be replaced by oxygen, nitrogen or sulfur atom;

5        Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is substituted at the end with cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.

3.        The method as described in Claim 1 wherein the 15-  
10        keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.

4.        The method as described in Claim 1 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-prostaglandin compound.

15        5.        The method as described in Claim 1 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-18-phenyl-19,20-dinor-prostaglandin compound.

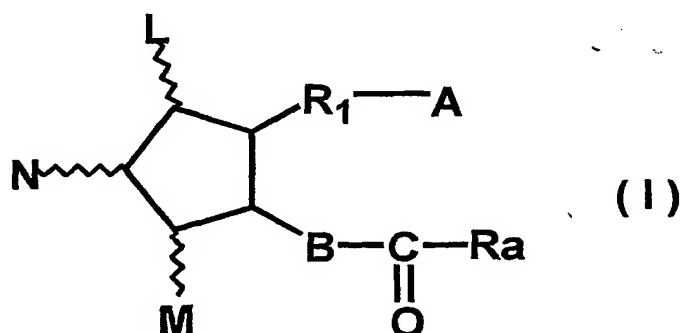
6.        The method as described in Claim 1 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-  
20        17-phenoxy-18,19,20-trinor-prostaglandin compound.

7.        An ophthalmic composition for treating ocular hypertension and glaucoma of a mammalian subject, comprising an effective amount of 15-keto-prostaglandin compound having a ring structure at the end of the w chain,  
25        wherein said composition is to be administered to the eyes

of the subject once a day.

8. The composition as described in Claim 7 wherein the 15-keto-prostaglandin compound is a compound represented by the following formula (I):

5



wherein L, M and N are hydrogen atom, hydroxy, halogen atom, lower alkyl, hydroxy(lower)alkyl or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

10

A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or a functional derivative thereof;

B is -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -C≡C-;

15 R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and one or more carbon atoms in the aliphatic hydrocarbon residue may optionally

20 be replaced by oxygen, nitrogen or sulfur atom; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is substituted at the end with cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.

5 9. The composition as described in Claim 7 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.

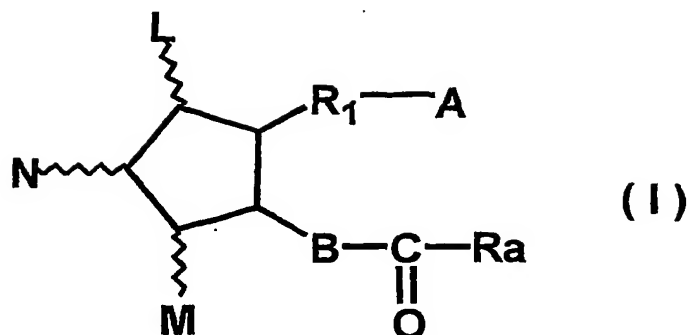
10 10. The composition as described in Claim 7 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-prostaglandin compound.

11. The composition as described in Claim 7 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-18-phenyl-19,20-dinor-prostaglandin compound.

15 12. The composition as described in Claim 7 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-17-phenoxy-18,19,20-trinor-prostaglandin compound.

20 13. Use of a 15-keto-prostaglandin compound having a ring structure at the end of the  $\omega$  chain for manufacturing an ophthalmic composition for treating ocular hypertension and glaucoma of a mammalian subject, wherein said composition is to be administered to the eyes of the subject once a day.

25 14. The use as described in Claim 13 wherein the 15-keto-prostaglandin compound is a compound represented by the following formula (I):



wherein L, M and N are hydrogen atom, hydroxy,  
 halogen atom, lower alkyl, hydroxy(lower)alkyl or oxo,  
 5 wherein at least one of L and M is a group other than  
 hydrogen, and the five-membered ring may have one or  
 more double bonds;

A is -CH<sub>2</sub>OH, -COCH<sub>2</sub>OH, -COOH or a functional  
 derivative thereof;

10 B is -CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH- or -C≡C-;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or  
 medium aliphatic hydrocarbon residue, which is  
 unsubstituted or substituted with halogen, alkyl, hydroxy,  
 oxo, aryl or heterocyclic group, and one or more carbon  
 15 atoms in the aliphatic hydrocarbon residue may optionally  
 be replaced by oxygen, nitrogen or sulfur atom; and

Ra is a saturated or unsaturated lower or medium  
 aliphatic hydrocarbon residue, which is substituted at the  
 end with cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl,  
 20 aryloxy, heterocyclic group or heterocyclic-oxy group.

15. The use as described in Claim 13 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.

5 16. The use as described in Claim 13 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-17-phenyl-18,19,20-trinor-prostaglandin compound.

17. The use as described in Claim 13 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-18-phenyl-19,20-dinor-prostaglandin compound.

10 18. The use as described in Claim 13 wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-17-phenoxy-18,19,20-trinor-prostaglandin compound.



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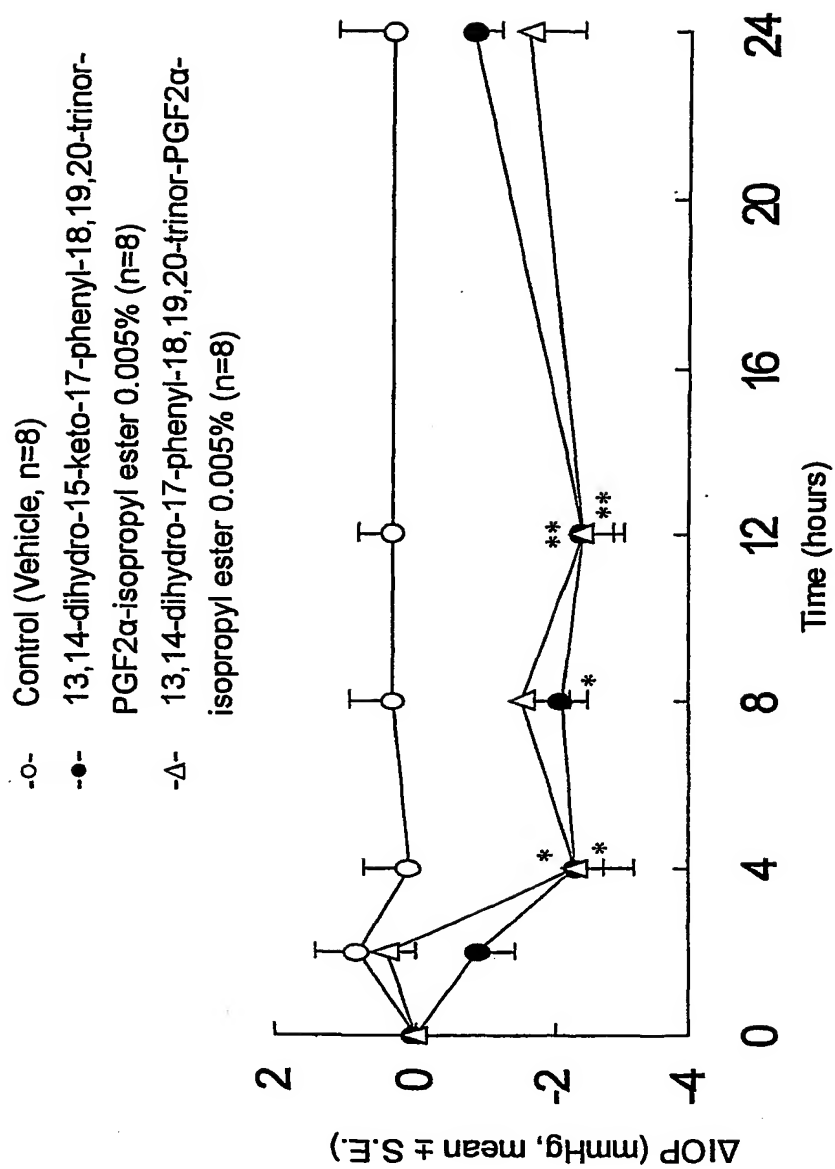


FIGURE 1

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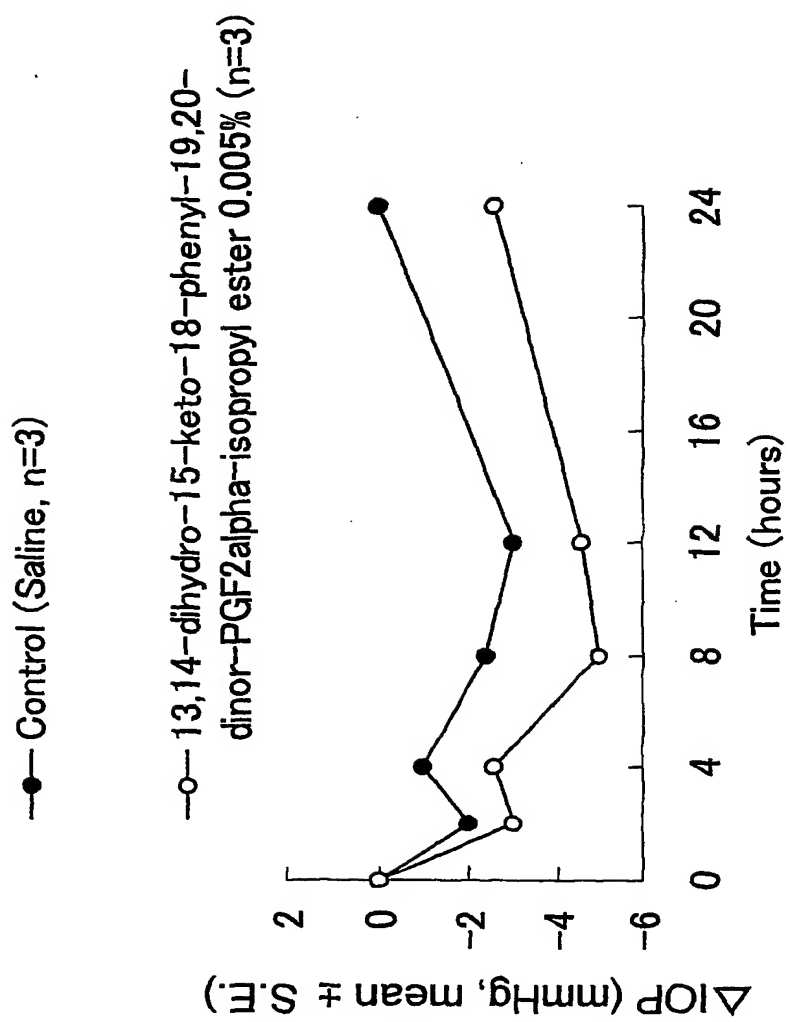


FIGURE 2

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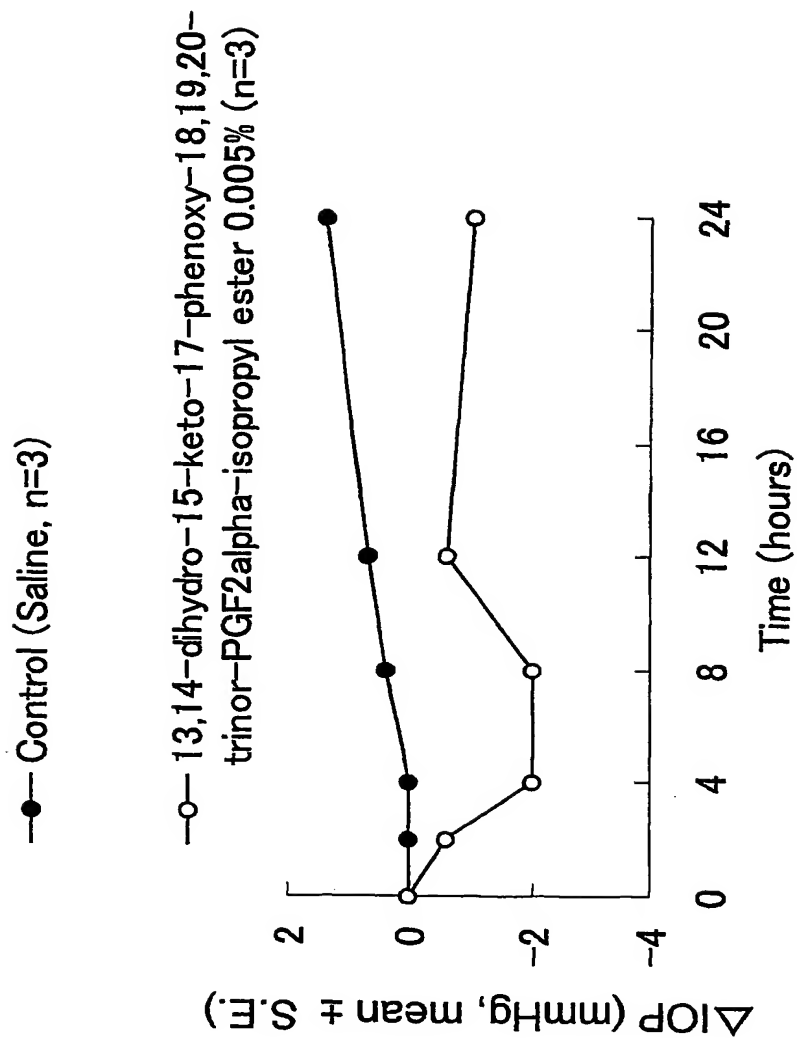


FIGURE 3

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 02/08446

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 366 279 A (UENO SEIYAKU OYO KENKYUJO KK) 2 May 1990 (1990-05-02) page 5, line 35 - line 41 page 6, line 1 -page 7, line 2 ---	1-18
X	US 6 030 999 A (STJERNSCHANTZ JOHAN WILHELM ET AL) 29 February 2000 (2000-02-29) column 13, line 6 - line 10 column 13, line 48 - line 57 ---	1-18
X	WO 97 23225 A (ALCON LAB INC) 3 July 1997 (1997-07-03) claim 1 page 10, line 5 -page 11, line 3 ---	1-18
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

18 October 2002

Date of mailing of the international search report

07/11/2002

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Authorized officer

Beranová, P

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 02/08446

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 212 200 A (UENO RYUZO ET AL) 18 May 1993 (1993-05-18) claims 1-3 -----	1-18
X	EP 0 458 588 A (UENO SEIYAKU OYO KENKYUJO KK) 27 November 1991 (1991-11-27) claim 1 page 3, line 55 -page 4, line 47 -----	1-18
X	EP 0 667 160 A (ALCON LAB INC) 16 August 1995 (1995-08-16) claim 14 -----	1-3,7-9, 13-15

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 7 and 13

Present claims 1, 7 and 13 relate to an extremely large number of possible compounds/methods. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the 15-keto-prostaglandins of formula I.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 02/08446

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1 - 6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1, 7 and 13  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; It is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 02/08446

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0366279	A	02-05-1990	JP 2008226 C	11-01-1996
			JP 2096528 A	09-04-1990
			JP 7039343 B	01-05-1995
			JP 2009965 C	02-02-1996
			JP 2096529 A	09-04-1990
			JP 7039344 B	01-05-1995
			AT 111736 T	15-10-1994
			AT 162074 T	15-01-1998
			DE 68918391 D1	27-10-1994
			DE 68918391 T2	19-01-1995
			DE 68928551 D1	19-02-1998
			DE 68928551 T2	23-04-1998
			EP 0366279 A2	02-05-1990
			EP 0580268 A2	26-01-1994
			US 6420422 B1	16-07-2002
			US 5194429 A	16-03-1993
			US 5236907 A	17-08-1993
US 6030999	A	29-02-2000	US 5422368 A	06-06-1995
			AT 101342 T	15-02-1994
			AU 625096 B2	02-07-1992
			AU 4189889 A	02-04-1990
			DE 68913000 D1	24-03-1994
			DE 68913000 T2	16-06-1994
			DK 112190 A	04-05-1990
			EP 1225168 A2	24-07-2002
			EP 1224934 A2	24-07-2002
			EP 1224935 A2	24-07-2002
			EP 0364417 A1	18-04-1990
			EP 0569046 A1	10-11-1993
			ES 2062102 T3	16-12-1994
			FI 92690 B	15-09-1994
			HK 159095 A	20-10-1995
			HU 9500316 A3	28-09-1995
			JP 10081624 A	31-03-1998
			JP 2955213 B2	04-10-1999
			JP 8109132 A	30-04-1996
			JP 2721414 B2	04-03-1998
			JP 3501025 T	07-03-1991
			WO 9002553 A1	22-03-1990
			US 5422369 A	06-06-1995
			US 5578618 A	26-11-1996
			US 5849791 A	15-12-1998
			US 5627208 A	06-05-1997
			US 6429226 B1	06-08-2002
			US 2001014693 A1	16-08-2001
			US 5296504 A	22-03-1994
			US 5321128 A	14-06-1994
			SE 8803855 A	28-10-1988
			US 6187813 B1	13-02-2001
WO 9723225	A	03-07-1997	AU 7680096 A	17-07-1997
			WO 9723225 A1	03-07-1997
			US 6166073 A	26-12-2000
US 5212200	A	18-05-1993	AT 72235 T	15-02-1992
			AT 82499 T	15-12-1992
			AT 108330 T	15-07-1994



**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International Application No  
PCT/JP 02/08446

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5212200, A		AU 600168 B2	02-08-1990
		AU 2231388 A	23-03-1989
		CA 1324129 A1	09-11-1993
		CA 1328075 A1	29-03-1994
		DE 3850676 D1	18-08-1994
		DE 3868127 D1	12-03-1992
		DE 3876050 D1	24-12-1992
		DE 3876050 T2	25-03-1993
		EP 0289349 A1	02-11-1988
		EP 0308135 A2	22-03-1989
		EP 0455264 A2	06-11-1991
		ES 2032016 T3	01-01-1993
		ES 2052735 T3	16-07-1994
		GB 2209939 A, B	01-06-1989
		GR 3003749 T3	16-03-1993
		GR 3006319 T3	21-06-1993
		JP 2592204 B2	19-03-1997
		JP 6080571 A	22-03-1994
		JP 1151552 A	14-06-1989
		JP 1941635 C	23-06-1995
		JP 6067900 B	31-08-1994
		JP 1858208 C	27-07-1994
		JP 2000108 A	05-01-1990
		JP 5071567 B	07-10-1993
		KR 9306202 B1	08-07-1993
		KR 9300051 B1	06-01-1993
		NZ 226197 A	25-02-1992
		US 5001153 A	19-03-1991
		US 5591887 A	07-01-1997
		US 6420422 B1	16-07-2002
		US 5106869 A	21-04-1992
		US 5151444 A	29-09-1992
		US 5770759 A	23-06-1998
		US 5166178 A	24-11-1992
		US 5221763 A	22-06-1993
		ZA 8806871 A	30-05-1989
		ZA 8806872 A	26-07-1989
		ZA 8806909 A	30-05-1989
		OA 9028 A	31-03-1991
EP 0458588 A	27-11-1991	AT 114470 T	15-12-1994
		CA 2042972 A1	23-11-1991
		DE 69105349 D1	12-01-1995
		DK 458588 T3	13-03-1995
		EP 0458588 A1	27-11-1991
		ES 2067864 T3	01-04-1995
		JP 4253910 A	09-09-1992
		JP 7098751 B	25-10-1995
		US 5208256 A	04-05-1993
EP 0667160 A	16-08-1995	US 5721273 A	24-02-1998
		AT 216889 T	15-05-2002
		AU 687906 B2	05-03-1998
		AU 7913894 A	22-06-1995
		CA 2138181 A1	16-06-1995
		DE 69430521 D1	06-06-2002
		EP 1088816 A2	04-04-2001
		EP 0667160 A2	16-08-1995

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International Application No  
PCT/JP 02/08446

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0667160 . A		JP 2769294 B2	25-06-1998
		JP 10120572 A	12-05-1998
		US 2002107414 A1	08-08-2002
		US 6344581 B1	05-02-2002
		US 5627209 A	06-05-1997
		US 5807892 A	15-09-1998
<hr/>			